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EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 02/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/067,094	GADDAM ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2005 and 31 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-10,13,14,17,18,24,28,30,34,36,40,42,48,52,60 and 64-69* is/are pending in the application.

4a) Of the above claim(s) *3-10,64 and 65* is/are withdrawn from consideration.

5)☒ Claim(s) *1,13,14,17,18 and 66-69* is/are allowed.

6)☒ Claim(s) *24,28,30,34,36,40,42,48,52,58 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/4/04 & 7/27/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to amendments filed on 10/6/05 and 10/31/05. Applicant has amended claims 1, 13, 14, 24, 28, 30, 34, 48, and 52. Applicant has canceled claims 2, 11, 12, 15, 16, 19-23, 25-27, 29, 31-33, 35, 37-39, 41, 43-47, 49-51, 53-55, 57-59, and 61-63. Claims 66-69 are new. Claims 1, 13, 14, 17, 18, 24, 28, 30, 34, 36, 40, 42, 48, 52, 56, and 60-63 were previously rejected. There are thirty claims pending and twenty under consideration. Claims 1, 11, and 66-69 are compound claims. Claims 13, 14, 17, and 18 are composition claims. Claims 24, 28, 30, 34, 36, 40, 42, 48, 52, 56, and 60 are method of using claims. This is the third action on the merits. The application concerns some α-ethoxybenzenepropanoic acid compounds, compositions, and uses thereof.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/05 has been entered.

Response to Amendment

3. Applicants' cancellation of claims 20-23 renders moot the duplicate claim objection made in point #4 of the Final Rejection. Applicants' deletion of solvates

and polymorphs from the claims overcomes the enablement rejection made in point #5 of that action. Applicants' limitation of claim 1 to fifteen specific salts overcomes the art rejection over Das ('816) made in point #7 of that action. While Das ('816) teaches metal, lysine, guanidine, bisethanolamine, and arginine salts of the presently claimed acids, it does not mention or make obvious the presently claimed slats. Similarly, the art rejections over Gurram ('067) and Lohray (WO 99/8501 A2) made in points #8 and #9 are overcome.

Election/Restrictions

4. Claims 3-10, 64, and 65 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** effective traverse in the reply filed on 3/4/04.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24, 28, and 48 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specification does not set forth any steps involved in determining how to identify "diseases in which insulin resistance is the underlying pathophysiological mechanism". It is unclear

what diseases and treatments applicant is intending to encompass. Determining whether a given disease responds or does not respond to such a insulin agonist or potentiator and thus, covered by the claim language, will require extensive and potentially inconclusive clinical research. With out such clinical research to identify the patients and diseases Applicants intend to treat, the physician skilled in the clinical arts cannot determine the metes and bounds of the claim. Hence, the claims are indefinite. Paragraph [00009], which spans pages 3-4, lists eight specific diseases but uses open terms, "includes". What additional diseases are covered by the rejected claims?

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24, 28, 30, 34, 36, 40, 42, 48, 52, 56, and 60 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating type II diabetes, insulin resistance, psoriasis, and hypercholesteremia, does not reasonably provide enablement for treating the lengthy list of other claimed diseases. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process

claims, refers to operability and how to make the claimed process work. The factors to be considered in making an enablement rejection have been summarized above. The four main issues are the lack of any correlation between clinical efficacy for disease treatment and Applicants' one *in vitro* assay and two *in vivo* assays, the narrow scope of working data present, the state of the prior art, and the breadth of the claims.

a) Determining if any particular claimed compound would treat any particular claimed disease would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different diseases described below, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large quantity of experimentation. b) The direction concerning treating human diseases is found in paragraph [00016], spanning pages 7 to 8, which merely states Applicants' intention to do so. Applicants describe formulations in the passage spanning paragraph [000232], page 36 to paragraph [000240], page 39. Doses required to practice their invention are described in paragraph [000241], page 39. A 10,000-fold range of doses is recommended. Since no PPARγ receptor agonist has ever been used to treat IBD, arteriosclerosis, obesity, inflammation, or cancer,

how is the skilled physician to know what dose to use for each of these different diseases?

There is an *in vitro* assay, drawn to hPPAR$_\gamma$, described in the passage spanning paragraph 449, page 98 to paragraph 451, page 99 with data on eight compounds. There is an *in vivo* assay, drawn to glucose reduction in mice, described in the passage spanning paragraph 453, page 100 to paragraph 458, page 101 with data on a single compound. There is an *in vivo* assay, drawn to cholesterol reduction in mice, described in the passage spanning paragraph 466, page 103 to paragraph 468, page 103 with data on seven compounds. Applicants do not state and it is not recognized in the pharmacological arts these three assays are correlated to clinical efficacy for the treatment of IBD, arteriosclerosis, and cancer, for example. There is a prophetic HMGCo enzyme assay and there are three prophetic diabetes, cholesterol lowering in the mouse, and obesity assays also described. None of Applicants compounds appear to have been tested for these therapeutic indications.

c) There is no working example of treatment of any disease in man or animals. There is no working example of any pharmaceutical formulation, which would be required by the physician to practice Applicants therapeutic claims. d)

The nature of the invention is clinical treatment of disease with agonists of the PPARγ receptor, which involves physiological activity.

e) The state of the clinical arts in PPARγ related diseases is provided by Cobb (Ann. Reports Med. Chem.) that antidiabeteic efficacy has been correlated to affinity to the PPARγ binding site, in the first paragraph, page 216. Sapone (Pharmacogenetics) reports that mice lacking any PPARα receptors develop normally. In his abstract he says that "[t]he biological significance of these novel PPARalpha alleles remains to be established".

The state of the art of clinical oncology is no compound has yet shown clinical efficacy against every type of cancer. To quote Salmon (Principles of Cancer Therapy) in the paragraph on page 1038 titled "Medical Therapy", "[c]urative therapy has been developed for a series of relatively uncommon neoplasms and useful palliative therapy has been developed for some common forms of cancer (Table 162-4). With rare exceptions, effective therapy has utilized combinations of anticancer drugs." Applicant's attention is drawn to Tables 162-6, 162-7, 162-8, 162-162-9, 162-10, and the material on pages 1045-1046 titled "Miscellaneous Anticancer Agents" in Salmon (Principles of Cancer Therapy). Different agents are used for different specific forms of cancer and no single agent is listed as a treatment of every single type of cancer. To quote Balasubramanian

(Recent Developments in Cancer Cytotoxics) from page 151 first paragraph "[t]he successful treatment of solid tumors remains a formidable challenge. The partial success of traditional cancer chemotherapy...". On page 158, second paragraph Balasubramanian (Recent Developments in Cancer Cytotoxics) states: "The future scenario in clinical management of cancer will be mainly dictated by the availability of less toxic and tumor selective agents". No compound has shown clinical efficacy against all cancers, thus no *in vivo* or *in vitro* assay could be validated for the identification of such a general agent. Applicants' specification logically must lack such assay data.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under

varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there was no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain).

h) The scope of the claims involves all of the hundreds of thousands of compounds of claim 1 as well as the dozens of named diseases including obesity, arthrosclerosis, coronary artery disease, psoriasis, inflammatory bowel disease, cancer generally, and inflammation generally. Cancer is just an umbrella term Cancers vary from those so benign that they are never treated to those so virulent that all present therapy is useless. The present specification says, in effect: here are the compounds and how to make them. You figure out what cancers they might be useful against. This is not the "immediate benefit to the public" required by *Cross et al. v. Iizuka et al* 224 USPQ 739, and *Nelson v. Bowler* 206 USPQ 881.

According to Stedman there over two hundred such cancerous conditions, including, "acinar cell tumors a solid and cystic tumors of the pancreas, occurring in young women; tumors cells contain zymogen granules. Acoustic tumors,

vestibular schwannoma, acute splenic tumors acute splenitis, enlargement, and softening of the spleen, usually due to bacteremia or severe bacterial toxemia. Adenoid tumors adenoma, or neoplasm with gland like spaces. Adenomatoid tumors a small benign tumors of the male epididymis and female genital tract, consisting of fibrous tissue or smooth muscle enclosing anastomosing gland-like spaces containing acid mucopolysaccharide lined by flattened cells that have ultra-structural characteristics of mesothelial cells, benign mesothelioma of genital tract tumors, adenomatoid odontogenic tumors a benign epithelial odontogenic tumors appearing radiographically as a well-circumscribed, radiolucent-radiopaque lesion usually surrounding the crown of an impacted tooth in an adolescent or young adult; characterized histologically by columnar cells organized in a duct like configuration interspersed with spindle-shaped cells and amyloidlike deposition that gradually undergoes dystrophic calcification, adenoameloblastoma, ameloblastic adenomatoid tumors. Adipose tumors, lipoma, ameloblastic adenomatoid tumors, adenomatoid odontogenic tumors. Amyloid tumors, nodular amyloidosis, aortic body tumors, chemodectoma, Bednar tumors, pigmented dermatofibrosarcoma protuberans. Benign tumors, tumors that do not form metastases and does not invade and destroy adjacent normal tissue, innocent tumors. Blood tumors term sometimes used to denote an aneurysm, hemorrhagic

cyst, or hematoma. Borderline ovarian tumors an ovarian surface epithelial tumors in which the growth pattern is intermediate between benign and malignant; includes mucinous, serous, endometrioid, and Brenner tumors of the ovary; highly curable but may recur after surgical removal, low malignant potential tumors. Brenner tumors a relatively infrequent benign neoplasm of the ovary, consisting chiefly of fibrous tissue that contains nests of cells resembling transitional type epithelium, as well as gland-like structures that contain mucin; origin is controversial, but it may arise from the Walthard cell rest; ordinarily found incidentally in ovaries removed for other reasons, especially in postmenopausal women. Brooke tumors, trichoepithelioma, brown tumors a mass of fibrous tissue containing hemosiderin-pigmented macrophages and multinucleated giant cells, replacing and expanding part of a bone in primary hyperparathyroidism. Calcifying epithelial odontogenic tumors a benign epithelial odontogenic neoplasm derived from the stratum intermedium of the enamel organ; a painless, slowly growing, mixed radiolucent-radiopaque lesion characterized histologically by cords of polyhedral epithelial cells, deposits of amyloid, and spherical calcifications, Pindborg tumors. Carcinoid tumors a usually small, slow-growing neoplasm composed of islands of rounded, oxyphilic, or spindle-shaped cells of medium size, with moderately small vesicular nuclei, and covered by intact

mucosa with a yellow cut surface; neoplastic cells are frequently palisaded at the periphery of the small groups, and the latter have a tendency to infiltrate surrounding tissue. Such neoplasms occur anywhere in the gastrointestinal tract (and in the lungs and other sites), with approximately 90% in the appendix and the remainder chiefly in the ileum, but also in the stomach, other parts of the small intestine, the colon, and the rectum; those of the appendix and small tumors seldom metastasize, but reported incidences of metastases from other primary sites and from tumors exceeding 2.0 cm in diameter vary from 25-75%; lymph nodes in the abdomen and the liver may be conspicuously involved, but metastases above the diaphragm are rare. Carcinoid syndrome, carotid body tumors, chemodectoma. Cellular tumors, tumors composed mainly of closely packed cells. Cerebellopontine angle tumors, vestibular schwannoma. Chromaffin tumors, chromaffinoma. Codman tumors chondroblastoma of the proximal humerus. Collision tumors two originally separate tumors, especially a carcinoma and a sarcoma, that appear to have developed by chance in close proximity, so that an area of mingling exists, carcinosarcoma. Connective tumors any tumors of the connective tissue group, such as osteoma, fibroma, and sarcoma. Dermal duct tumors a benign small tumors derived from the intradermal part of eccrine sweat gland ducts occurring often on the head and neck. Dermoid tumors, dermoid

cystumors desmoid tumors, desmoplastic small cell tumors a high-grade malignant tumors found most often in the abdomen of adolescent males; typically tumors cells contain both desmin and keratin, i.e., show hybrid features like fetal mesothelial cells; the exact nature of these cells remains unknown. Dysembryoplastic neuroepithelial tumors a rare low-grade neoplasm most frequently seen in children and associated with seizures and cortical dysplasia, the often multinodular, multicystic tumors is composed of oligodendroglial-like cells with accompanying neurons. Eighth nerve tumors, vestibular schwannoma. Embryonal tumors, embryonic tumors a neoplasm, usually malignant, which arises during intrauterine or early postnatal development from an organ rudiment or immature tissue; it forms immature structures characteristic of the part from which it arises, and may form other tissues as well. The term includes neuroblastoma and Wilms tumors, and is also used to include certain neoplasms presenting in later life, this usage being based on the belief that such tumors arise from embryonic rests. Teratoma, embryoma, embryonal tumors of ciliary body, embryonal medulloepithelioma. Endocervical sinus tumors malignant germ cell tumors commonly found in the ovary. The tumor arises from primitive germ cells and develops into extra-embryonic tissue resembling the yolk sac, yolk sac carcinoma. Endodermal sinus tumors a malignant neoplasm occurring in the gonads, in

sacrococcygeal teratomas, and in the mediastinum; produces □-fetoprotein and is thought to be derived from primitive endodermal cells, yolk sac tumors. Endometrioid tumors a tumors of the ovary containing epithelial or stromal elements resembling tumors of the endometrium. Erdheim tumors, craniopharyngioma, Ewing tumors a malignant neoplasm which occurs usually before the age of 20 years, about twice as frequently in males, and in about 75% of patients involves bones of the extremities, including the shoulder girdle, with a predilection for the metaphysis; histologically, there are conspicuous foci of necrosis in association with irregular masses of small, regular, rounded, or ovoid cells (2-3 times the diameter of erythrocytes), with very scanty cytoplasm, endothelial myeloma, Ewing sarcoma. Fecal tumors, fecaloma, fibroid tumors old term for certain fibromas and leiomyomas. Gastrointestinal autonomic nerve tumors benign or malignant tumors of stomach and small intestine histogenetically related to myenteric plexus; may be familial and related to gastrointestinal neuronal dysplasia. Gastrointestinal stromal tumors benign or malignant tumors composed of unclassifiable spindle cells; immunohistochemically distinct from smooth muscle and Schwann cell tumors. Giant cell tumors of bone a soft, reddish-brown, sometimes malignant, osteolytic tumors composed of multinucleated giant cells and ovoid or spindle-shaped cells, occurring most

frequently in an end of a long tubular bone of young adults, giant cell myeloma, osteoclastoma. Giant cell tumors of tendon sheath a nodule, possibly inflammatory in nature, arising commonly from the flexor sheath of the fingers and thumb; composed of fibrous tissue, lipid- and hemosiderin-containing macrophages, and multinucleated giant cells, localized nodular tenosynovitis. Glomus tumors, a vascular neoplasm composed of specialized pericytes (sometimes termed glomus cells), usually in single encapsulated nodular masses that may be several millimeters in diameter and occur almost exclusively in the skin, often subungually in the upper extremity; it is exquisitely tender and may be so painful that patients voluntarily immobilize an extremity, sometimes leading to atrophy of muscles; multiple glomus tumors occur, sometimes with autosomal dominant inheritance. Tumors with cavernous spaces lined by glomus cells are called glomangiomas. Glomus jugulare tumors a glomus tumors arising from the jugular glomus and usually presenting initially in the hypotympanum. Glomus tympanicum tumors a glomus tumors arising on the medial wall of the middle ear. Godwin tumors, benign lymphoepithelial lesion. Granular cell tumors a microscopically specific, generally benign tumors, often involving peripheral nerves in skin, mucosa, or connective tissue, derived from Schwann cells; the abundant cytoplasm contains lysosomal granules, the cells infiltrate between adjacent tissues although growth is

slow, and adjacent surface epithelium may show hyperplasia. Granulosa cell tumors a benign or malignant tumors of the ovary arising from the membrana granulosa of the vesicular ovarian (graafian) follicle and frequently secreting estrogen; it is soft, solid, white or yellow, and consists of small round cells sometimes enclosing Call-Exner bodies; larger lipid-containing cells may be present, folliculoma, Grawitz tumors old eponym for renal adenocarcinoma, heterologous tumors a tumors composed of a tissue unlike that from which it springs. Hilar cell tumors of ovary, steroid cell tumors. Histoid tumors old term for a tumors composed of a single type of differentiated tissue. Homologous tumors, a tumors composed of tissue of the same sort as that from which it springs, innocent tumors, benign tumors, interstitial cell tumors of testis, Leydig cell tumors. Islet cell tumors an endocrine tumors composed of cells equivalent or related to those in the normal islet of Langerhans; may be benign or malignant; usually hormonally active; comprises insulinomas, glucagonomas, vipomas, somatostatinomas, gastrinomas, pancreatic polypeptide-secreting tumors, and multihormonal or hormonally inactive pancreatic islet cell tumors. Juxtaglomerular cell tumors a tumors of juxtaglomerular cell origin usually presenting with symptoms of secondary aldosteronism, including severe diastolic hypertension, which appears to be due to tumors-produced renin. The histological

appearance resembles that of a hemangiopericytoma. Klatskin tumors adenocarcinoma located at the bifurcation of the common hepatic duct, Krukenberg tumors a metastatic carcinoma of the ovary, usually bilateral and secondary to a mucous carcinoma of the stomach, which contains signet-ring cells filled with mucus. Landschutz tumors a transplantable, possibly isoantigenic, highly virulent neoplasm which can be grown in any strain of mice; the host is killed in a few days by what is apparently an anaplastic carcinoma. Leydig cell tumors a testicular and, less commonly, ovarian neoplasm composed of Leydig cells, usually benign but may be malignant; may secrete androgens or estrogens, interstitial cell tumors of testis. Lindau tumors, hemangioblastoma, low malignant potential tumors, borderline ovarian tumors. Malignant tumors a tumors that invades surrounding tissues, is usually capable of producing metastases, may recur after attempted removal, and is likely to cause death of the host unless adequately treated. Malignant mixed Müllerian tumors (MMMT), mixed mesodermal tumors. Melanotic neuroectodermal tumors of infancy a benign neoplasm of neuroectodermal origin that most often involves the anterior maxilla of infants in the first year of life. It presents clinically as a rapidly growing blue-black lesion producing a destructive radiolucency; histologically, it is characterized by small, round, undifferentiated tumors cells interspersed with larger polyhedral melanin-

producing cells arranged in an alveolar configuration, melanoameloblastoma, pigmented ameloblastoma, pigmented epulis, progonoma of jaw, retinal anlage tumors. Merkel cell tumors a rare malignant cutaneous tumors seen in sun-exposed skin of elderly patients composed of dermal nodules of small round cells with scanty cytoplasm in a trabecular pattern; the tumors cells contain cytoplasmic dense core granules resembling neurosecretory granules seen in Merkel cells, primary neuroendocrine carcinoma of the skin, trabecular carcinoma, mesonephroid tumors, mesonephroma, mixed tumors, a tumors composed of two or more varieties of tissue, mixed mesodermal tumors a sarcoma of the body of the uterus arising in older women, composed of more than one mesenchymal tissue, especially including striated muscle cells, malignant mixed Müllerian tumors. Mixed tumors of salivary gland a tumors composed of salivary gland epithelium and fibrous tissue with mucoid or cartilaginous areas, pleomorphic adenoma. Mixed tumors of skin, chondroid syringoma. Mucoepidermoid tumors, mucoepidermoid carcinoma. Nelson tumors a pituitary tumors causing the symptoms of Nelson syndrome, oil tumors, lipogranuloma, oncocytic hepatocellular tumors, fibrolamellar liver cell carcinoma, organoid tumors a tumors of complex structure, glandular in origin, containing epithelium, connective tissue, etc. Pancoast tumors any carcinoma of the lung apex causing the Pancoast

syndrome by invasion or compression of the brachial plexus and stellate ganglion, superior pulmonary sulcus tumors. Papillary tumors, papilloma, paraffin tumors, paraffinoma, phantom tumors accumulation of fluid in the interlobar spaces of the lung, secondary to congestive heart failure, radiologically simulating a neoplasm. Phyllodes tumors a spectrum of neoplasms consisting of a mixture of benign epithelium and stroma with variable cellularity and cytologic abnormalities, ranging from benign phyllodes tumors to cytosarcoma phyllodes; most often involves the breast tumors pilar tumors of scalp a solitary tumors of the scalp in elderly women that may ulcerate; microscopically resembles squamous cell carcinoma composed of glycogen-rich clear cells, but is benign, proliferating tricholemmal cystumors Pindborg tumors, calcifying epithelial odontogenic tumors. Pinkus tumors, fibroepithelioma. Placental site trophoblastic tumors a tumors usually arising in the uterus of parous women during reproductive years. Histologically, the tumors consist of a predominance of intermediate trophoblastic cells with fibrinoid material and vascular invasion. Pontine angle tumors a tumors in the angle formed by the cerebellum and the lateral pons, often refers to an acoustic schwannoma. Potato tumors of neck a firm nodular mass in the neck, usually a carotid body tumors (chemodectoma). Pregnancy tumors, granuloma gravidarum, primitive neuroectodermal tumors a designation used to refer to a

group of morphologically similar embryonal neoplasms that arise in intracranial and peripheral sites of the nervous system and which may show various degrees of cellular differentiation; includes medulloblastoma, pineoblastoma, etc. ranine tumors, ranula, Rathke pouch tumors, craniopharyngioma. Retinal anlage tumors, melanotic neuroectodermal tumors of infancy. Rous tumors, Rous sarcoma. Sand tumors, psammomatous meningioma. Sertoli cell tumors a tumors of testis or ovary composed of Sertoli cells; most often benign but may be malignantumors Sertoli-Leydig cell tumors an ovarian tumors composed of Sertoli and Leydig cells; may secrete androgens, arrhenoblastoma, gynandroblastoma. Sertoli-stromal cell tumors a generic term for ovarian sex-cord stromal tumors composed of Sertoli cells, Leydig cells, and cells resembling rete epithelial cells, either in a pure form or as a mixture of these cell types. Solitary fibrous tumors a benign tumors of fibrous tissue that usually arises in the pleural space on other sites, benign mesothelioma. Squamous odontogenic tumors a benign epithelial odontogenic tumors thought to arise from the epithelial cell rests of Malassez; appears clinically as a radio lucent lesion closely associated with the tooth root and histologically as islands of squamous epithelium enclosed by a peripheral layer of flattened cells. Steroid cell tumors a collective term used for ovarian tumors composed of cells resembling steroid-secreting lutein cells; comprises several tumors such as stromal

luteoma, Leydig cell tumors, steroid cell tumors not otherwise specified; hormonally active; may be benign or malignantumors, hilar cell tumors of ovary. Sugar tumors a benign clear cell tumors of the lung containing abundant glycogen. Superior pulmonary sulcus tumors, Pancoast tumors, teratoid tumors, teratoma, theca cell tumors, thecoma. Triton tumors a peripheral nerve tumors with striated muscle differentiation, seen most often in neurofibromatosis; named after the Masson theory of transformation of motor nerve fibers into muscle in triton salamanders. Turban tumors multiple cylindromas of the scalp which, when overgrown, may resemble a turban, villous tumors, villous papilloma, Warthin tumors, adenolymphoma, Wilms tumors a malignant renal tumors of young children, composed of small spindle cells and various other types of tissue, including tubules and, in some cases, structures resembling fetal glomeruli, and striated muscle and cartilage. Often inherited as an autosomal dominant trait, nephroblastoma, yolk sac tumors, endodermal sinus tumors, Zollinger-Ellison tumors a non-beta cell tumors of pancreatic islets causing the Zollinger-Ellison syndrome."

Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to

recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages that have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.

Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the

eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics.

Cholecystitis is gallbladder inflammation usually caused by a gallstone that cannot pass through the cystic duct. In those cases, it normally cannot be treated by pharmaceuticals but instead the gallbladder is removed. Cholecystitis without the formation of gallstones, called acalculous cholecystitis, is caused by bacteria such as Salmonella, Staphylococcus, Streptococcus (as part of scarlet fever), and leptospirosis, and thus may be treatable by treating the underlying infectious agent. Acute inflammation of the gall bladder can also arise from typhoid; treatment is with antibiotics.

In gout, joint inflammation is caused by the formation of monosodium urate monohydrate (MSU) crystals within the joint space. Acute attacks of gout are treated with colchicine (to inhibit of MSU-induced chemotactic factor release by PMNs) and after the acute phase with allopurinol to control the blood levels of uric acid. Pseudogout, sometimes referred to as calcium pyrophosphate disease (CPPD), is inflammation caused by calcium pyrophosphate (CPP) crystals. It is treated with nonsteroidal anti-inflammatory drugs, corticosteroids, and colchicine.

Sinusitis is the inflammation of the mucosal lining of one or more sinuses. It commonly accompanies upper respiratory viral infections and in most cases requires no treatment.

Pharyngitis (tonsillitis) is an inflammatory illness of the mucous membranes and underlying structures of the throat (nasopharynx, uvula, and soft palate). The illness can be caused by bacteria, viruses, mycoplasmas, fungi, and parasites, and uncertain causes, especially Streptococcus pyogenes, adenoviruses, influenza viruses, parainfluenza viruses, Epstein-Barr virus, enteroviruses, and Mycoplasma pneumoniae. Similarly, Osteomyelitis is the inflammation of bones, generally caused by bacteria (most commonly Staphylococcus Aureus). Fungi or viruses can cause the disease. Dacryoadenitis, an inflammation of the tear gland, can arise from infectious mononucleosis, mumps, gonorrhea, or influenza. Conjunctivitis (pink eye) is inflammation of the conjunctiva and can be caused by many microorganisms, including staphylococci, Haemophilus influenzae, streptococci, gonococci, and viruses such as adenoviruses. Treatment in all of these cases, when possible, is thus to the underlying infectious agent.

Rheumatoid arthritis is an inflammatory bone disease causing destruction of articular cartilage, in which macrophages accumulate in the rheumatoid synovial membrane. Mediators are cytokines, including IL-18 and IL-18, and IFN- .

Pneumonia is an inflammation of the lungs that can be caused by viruses (such as respiratory syncytial, parainfluenza, and influenza), bacteria, fungi, mycoplasmas, rickettsias (especially Q fever), Chlamydia, or parasites. It can also occur as a hypersensitivity, or allergic response, to agents such as mold, humidifiers, and animal excreta, and in such a case would be treated with anti-allergic agents.

Other inflammations in the respiratory system include CF, adult respiratory distress syndrome, asthma, and bronchitis.

Myocarditis is an inflammation of the muscular middle layer of the heart (myocardium) Viruses, bacteria, and noninfectious diseases can cause it. Treatment is primarily supportive e.g. drugs may be used to improve the heart's ability to contract and to remove extra fluids from the body. Unless the underlying infectious agent itself is treatable, this inflammation is not itself treated.

Glossitis is inflammation of the tongue. Local causes of glossitis include bacterial or viral infection, mechanical irritation or injury from burns, rough edges of teeth or dental and oral appliances, or other trauma; exposure to irritants (tobacco, alcohol, hot foods, or spices), and sensitization (to e.g. toothpaste, mouthwash, breath fresheners, dyes in candy, plastic in dentures or retainers) anemia and other B vitamin deficiencies, erythema multiform, pemphigus vulgaris,

syphilis, and other disorders. It can be inherited. Corticosteroids such as prednisone may be given to reduce the inflammation. Antibiotics, antifungal medications, or other antimicrobials may be prescribed if the cause of glossitis is an infection. Anemia and nutritional deficiencies must be treated, often by dietary changes or other supplements.

Meningitis is an inflammation of the outer covering of the brain and spinal cord. Virtually any known infectious agent can cause it. Thus, if it were caused by Haemophilus influenzae or Neisseria meningitis, the antibiotic derivative rifampin would be used.

Encephalitis is an inflammation of the brain itself. It is most often caused by a group of arboviruses. Treatment of encephalitis is largely supportive because no specific antiviral agents, except for that which works against herpes simplex virus, are available for therapy.

Hepatitis is an inflammation of the liver, usually caused by viral invasion, notably hepatitis A, B and C, but sometimes Epstein-Barr virus; herpes simplex viruses; measles, mumps, and chicken pox viruses; and cytomegaloviruses. Treatment, when possible, is with antivirals. Inflammation of the liver also takes the form of alcoholic hepatitis. Lupoid hepatitis is an autoimmune disorder.

Hemorrhoids are an enlarged or varicose condition of the hemorrhoidal veins and tissues around the anus, either internal or external. Anything that obstructs the free circulation of the blood in the portal system will give rise to hemorrhoids. Constipation, straining at stool, diarrhea, dysentery, rough toilet paper, uncleanness, pelvic tumors, displacement of the uterus and pregnancy are among the most common causes.

There is a series of inflammatory problems directly connected to neutrophil-endothelial cell adhesion (NECA). These include frostbite injury, bacterial meningitis, acute airway inflammation, allograft rejection, hemorrhagic shock, septic shock, ischemia, and reperfusion injuries.

Urethritis is an inflammation of the duct that leads from the bladder to the exterior of the body. It is often due to fecal contamination or irritation due to physical or chemical substances (e.g. introduction of foreign bodies into the urethra, bubble bath, or soap) or gonorrhea. Treatment may simply involve the withdrawal of the offending chemical agent, or the administration of antibiotics, when Neisseria gonorrhoeae is involved.

Inflammation can arise from the eruption of teeth in a child (teething).

Inflammation of the nails can arise from chronic paronychia, fungus (especially Candida albicans), trauma, impaired circulation, and dermatitis.

Bright's disease (or glomerulonephritis) is inflammation of the glomeruli and the nephrons, the structures in the kidney that produce urine. It usually results from an infection, such as a streptococcal infection, that occurs somewhere else in the body. There is no real treatment beyond relief of the symptoms.

Thyroiditis is an inflammation of the thyroid gland, and takes three forms. Hashimoto's Thyroiditis (chronic lymphocytic thyroiditis) is the most common type of thyroiditis. It is an autoimmune disorder, and treatment is to start thyroid hormone replacement. For De Quervain's Thyroiditis (subacute or granulomatous thyroiditis), treatment is usually bed rest and aspirin to reduce inflammation. Occasionally cortisone and thyroid hormone may be used. Silent Thyroiditis usually arises following pregnancy. Treatment is usually bed rest with beta-blockers.

Regional enteritis (Crohn's disease or ileitis) is an autoimmune disorder, which is associated with the presence of Mycobacterium paratuberculosis. It can affect any part of the gastrointestinal tract but most commonly affects the ileum. The inflammation is controlled primarily by regulation of diet, antibiotics if abscesses and fistulas are present, sometimes Prednisone and other corticosteroids, and surgery.

Stomatitis, inflammation of the mouth, and mucositis, inflammation of the mucosa can arise from sources as diverse as Candida albicans, dentures, chemotherapy, and radiation therapy to the head, neck or mouth ("Radiation mucositis"). It may be secondary to infection, trauma, systemic diseases or autoimmune mechanisms. These come in many forms, such as aphthous ulcers, Acute Necrotizing Ulcerative Gingivitis i.e. "trench mouth", and Lichen Planus. Herpetiform ulcers treatment has ranged from antibiotics, immunosuppressants and yogurt, to Lactobacillus capsules, tetracycline and systemic steroids. Palliative measures include topical anesthetics, Vitamin E, analgesics, and coating agents. Antiviral agents may be used if viral origin is established.

Pancreatitis is inflammation of the pancreas and can arise from abdominal trauma, or the formation of gallstones that obstruct the common bile duct. It can be associated with excessive ingestion of alcohol; with disorders such as cystic fibrosis or Reye's syndrome; or with scorpion stings. Infectious causes include mycoplasmas, Epstein-Barr viruses, Coxsackie viruses, leptospirosis, hepatitis viruses, mumps, congenital German measles, Ascaris worms, and syphilis. The inflammation per se is generally not treatable. Treatment is usually supportive and consists of the management of pain and intravenous feeding.

Neuroretinitis is inflammation of the retina and optic nerve of the eye ("optic neuritis"). It is often idiopathic. It frequently arises secondary to some kind of infection, such as Hepatitis B, HSV, EBV, influenza A, mumps, Coxsackie B, TB, salmonella, Lyme disease, syphilis, leptospirosis, Histoplasmosis, Toxoplasmosis, toxocara, Sarcoidosis, and cat-scratch disease. Treatment is thus to the underlying cause. For example, diffuse unilateral subacute neuroretinitis (DUSN) arises from nematodes deep in the retina or in the subretinal space. Anthelminthic treatment is then used. When the origin is Toxoplasmosis, then anti-Toxoplasma medications such as Pyrimethamine.

Other eye inflammations include scleritis and episcleritis, inflammation of tissues on the sclera; choroiditis, inflammation of the middle coat (choroid) of the eyeball, and uveitis, which is inflammation of the parts of the eyes that make up the iris.

Gastritis is inflammation to the stomach lining. Atrophic gastritis is characterized by the loss of the stomach cells that are responsible for manufacturing acid, pepsin, and intrinsic factor. This condition occurs in older people or those suffering from Helicobacter pylori. Erosive (hemorrhagic) gastritis occurs when shallow ulcers or sores develop on the upper layer of the stomach

lining, usually because of the excessive ingestion of a stomach irritant such as aspirin or alcohol.

There can also be mentioned appendicitis, which can occur when a hard piece of stool blocks the opening of the appendix, causing swelling and inflammation.

The great majority of skin problems involve some type of inflammation, such as response to physical injury (e.g. sunburn, ticks, abrasion, or a bee string), acute allergic contact dermatitis (such as poison ivy), and infections (such as boils and cold sores). Ingrown hairs, or pili incarnati, can cause acute pustular reactions. Cancerous lesions of the skin frequently show some degree of inflammatory response. The inflammation of acne is caused by leakage of sebum and keratin debris outside the distended pilosebaceous duct. The bacillus Propionibacterium acnes, which populate the lesions, may also contribute indirectly to this inflammation by metabolizing the sebum to produce irritant fatty acids. Inflammation in skin problems is usually the result of the release of chemical mediators in the skin, notably histamine, peptides (kinins) and fatty acids (prostaglandins and leukotrienes), that are formed enzymatically in response to e.g. injury. Medications designed to counteract inflammation in the skin may or may not antagonize the effects of the particular type of mediator involved, if that is

known. The inflammation can take many different forms, including redness, (from dilation of blood vessels); heat, (from increased blood flow); swelling (from leakage of fluid from the small blood vessels); whealing reactions (hives, nettle rash, urticaria) in which vascular changes predominate, and pain or itching. Blisters (from enzymes released from inflammatory cells, resident cells of the skin, or blood plasma components) can cause the breakdown of proteins responsible for the structural integrity of the skin, leading to serious inflammatory disorders such as pemphigus. In addition, the affected skin may feel indurated (hardened) because of the deposition of the coagulation protein fibrin and the infiltration by inflammatory blood cells (lymphocytes, histiocytes, and polymorphonuclear leukocytes).

Prostatitis, inflammation of the prostate, comes in several different forms, including those of bacterial origins, and those, which are not, including chronic abacterial prostatitis and asymptomatic inflammatory prostatitis. Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases.

The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms, and treatment (or lack thereof) for inflammation.

It establishes that it is not reasonable to any agent to be able to treat inflammation generally.

Thus, the scope of claims is very broad.

Reconsideration of all the evidence related to each of these factors, and based on the evidence as a whole, the specification, at the time the application was filed, would not have taught one skilled in the art how make the full scope of the claimed invention without undue experimentation. *In re Wright*, 27 USPQ2d 1510. Thus, undue experimentation will be required to determine if any particular claimed compound is, in fact, a treatment of any rejected disease.

Applicants point to paragraphs [0006] to [0013] and some previously cited references to overcome this rejection. The cited paragraphs list the intended diseases, list some references, which are not available to the Examiner, and offer speculation, " [t]his would be useful in the treatment of certain types of cancer, which express PPARγ and **could lead** (emphasis added) to a quite nontoxic chemotherapy". Substantiation of use and scope is required when the use is "speculative", "sufficiently unusual", or not provided in the specification, *Ex parte Jovanovics,* 211 USPQ 907, *In re Langer,* 183 USPQ 288, *Hoffman v. Klaus*, 9 USPQ2d 1657, and *Ex parte Powers*, 220 USPQ 924 concerning the type of testing needed to support *in vivo* use claims. Also see the MPEP § 2164.03 for

enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry.

There are abstracts of fourteen scientific articles submitted with the response of 3/3/04. Of these 14, only one Ellis (Arch Dermatol) reports on any clinical studies on any PPARγ activators. Ellis (Arch Dermatol) states that troglitazone is effective in the treatment of psoriasis. Thus, psoriasis has been added to the list of enabled diseases.

Allowable Subject Matter

7. Claims 1, 13, 14, 17, 18, and 66-69 are allowed.

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

10. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (571) 273-8300. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact James O. Wilson, acting SPE of Art Unit 1624, at (571)-272-0661.

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